Journal of Arrhythmia 28 (2012) 273–276

Contents lists available at SciVerse ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

Prevalence and significance of the early repolarization pattern in inferolateral leads in patients with Brugada syndrome: A single-center study

Kimie Ohkubo [a], Ichiro Watanabe [a,*], Yasuo Okumura [a], Masayoshi Kofune [a], Koichi Nagashima [a], Hiroaki Mano [a], Kazumasa Sonoda [a], Toshiko Nakai [a], Yuji Kasamaki [a], Atsushi Hirayama [a], Naokata Sumitomo [b], Tomohiro Nakayama [c]

[a] Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
[b] Department of Pediatrics, Nihon University School of Medicine, Tokyo, Japan
[c] Department of Laboratory Medicine, Nihon University School of Medicine, Tokyo, Japan

ARTICLE INFO

Article history:
Received 14 November 2011
Received in revised form
27 February 2012
Accepted 30 March 2012
Available online 23 May 2012

Keywords:
Brugada syndrome
Early repolarization syndrome
J wave
Sudden cardiac death

ABSTRACT

In this study, the prevalence and prognostic significance of the early repolarization (ER) pattern in the inferolateral leads in patients with Brugada syndrome were investigated. Clinical, genetic, and electrophysiological data were collected and analyzed from 69 individuals with either a spontaneous or drug-induced Brugada type 1 electrocardiogram (ECG) pattern. An ER pattern was defined as *J*-point elevation at least 0.1 mV from the baseline in at least 2 inferior or lateral leads. The presence of late potentials and inducibility of ventricular fibrillation (VF) by programmed stimulation were compared between patients with and without a *J* wave. Follow-up data, including outcome events, were obtained for all patients. An ER pattern was observed in the inferolateral leads in 6 patients with a spontaneous Brugada type 1 ECG pattern and in 1 patient with a drug-induced Brugada type 1 ECG pattern. There was no significant intergroup difference in symptoms, family history of sudden cardiac death, prevalence of late potentials, or inducibility of VF. No patient with the ER pattern developed a cardiac event during the mean follow-up period of 73.6 ± 38.1 months. The ER pattern in the inferolateral leads is not uncommon in Brugada syndrome; however, the presence of a *J* wave does not appear to be associated with subsequent arrhythmic events in patients with Brugada syndrome.

1. Introduction

The early repolarization (ER) pattern, or *J* wave, is considered to be a benign electrocardiographic phenomenon affecting 2%–5% of the general population, and is most commonly observed in young men [1–3]. However, recent studies have shown a high incidence of the ER pattern confined to the inferolateral leads of patients with idiopathic ventricular fibrillation (VF) [4–6]. These studies, together with previous reports, indicate that ER syndrome may not be as benign as traditionally believed [7]. ER syndrome shares notable cellular and ionic similarities with Brugada syndrome, an autosomal dominant disease with incomplete penetrance characterized by *J*-point and ST-segment elevation in leads V_1–V_3 and a high propensity toward sudden cardiac death (SCD) [1,2,8]. Previous studies have examined the prognosis of Brugada syndrome in association with the ER pattern in inferolateral leads, but the results were controversial [9–11]. The retrospective, single center study described herein was carried out to further investigate the prevalence and prognostic significance of the ER pattern in the inferolateral leads of patients with Brugada syndrome.

2. Methods

2.1. Patients

The study group was comprised of 69 consecutive patients with a spontaneous or drug-induced (pilsicainide 1 mg/kg, intravenous [iv]) Brugada type 1 electrocardiogram (ECG) pattern recorded at Nihon University Hospital between 1996 and 2011. The diagnosis of Brugada syndrome was based on the ECG criteria recommended by the Second Consensus Conference of Brugada Syndrome [8]. Patients with complete right bundle branch block were not included in the study. All patients underwent transthoracic echocardiography, and 55 of the 69 patients underwent cardiac catheterization, coronary angiography, and left and right ventricular angiography. Laboratory tests were performed at the

* Correspondence address: Division of Cardiology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan.
E-mail address: iwatanab1953@gmail.com (I. Watanabe).

1880-4276/$ - see front matter © 2012 Japanese Heart Rhythm Society. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.joa.2012.03.016

outpatient clinic to exclude electrolyte or metabolic disturbances. The following clinical data were obtained from the patient records: age, sex, symptom(s), family history of SCD (<45 years of age), ECG pattern (type 1, type 2, or type 3 before the drug challenge test), and indication for implantable cardioverter-defibrillator (ICD). Patients with a previous history of syncope or presyncope, documented sustained ventricular arrhythmia, or aborted SCD were considered symptomatic. Patients with neurally mediated syncope established by the tilt table test were not considered symptomatic. Screening for sodium channel, voltage-gated, type V, alpha subunit (*SCN5A*) gene mutations was performed in 44 of the patients, according to our institutional guidelines for genetic research. The study protocol, including genetic analysis, electrophysiological study, and intravenous administration of pilsicainide, was approved by the Clinical Research Committee of Nihon University Hospital.

2.2. ECG ER pattern

In most cases, more than 1 ECG (median, 5; range, 3–7) was available for review from the index hospitalization and the outpatient clinic records. As previously described [4,6], ER was defined as ≥ 1 mm (0.1 mV) elevation of the QRS-ST junction (*J* point) in 2 or more contiguous inferior (II, III, and aVF) and/or lateral (I, aVL, V5, and V6) leads. ER was considered to be present if this criterion was met on any single ECG obtained during the index hospitalization.

2.3. Signal-averaged ECG

A ventricular signal-averaged electrocardiogram (ART 1200 EPX signal-averaged ECG apparatus, Arrhythmia Research Technology Inc., Austin, TX, USA; noise level <0.3 μV, with a bidirectional 4-pole Butterworth high pass filter-40 Hz) was recorded in 61 patients. A positive late potential is defined at our institution as a root mean square voltage of the last 40 ms <20 μV [13].

2.4. Electrophysiological study

A comprehensive electrophysiological study was performed after written informed consent was obtained. This study was conducted in a fasting, drug-free, and non-sedated state in 55 patients. After access to the right femoral vein was obtained at 2 sites, 2 steerable quadripolar catheters (6 F) with an interelectrode distance of $2-5-2$ mm (Biosense-Webster, Diamond Bar, CA, USA) were positioned in the right ventricle. Endocardial potentials were filtered to recording frequencies of 30–500 Hz and recorded on a Bard computer system (BARD Lab Pro, Bard Electrophysiology, Lowell, MA, USA). Programmed electrical stimulation from the right ventricular apex (RVA) and right ventricular outflow tract (RVOT) was performed at twice the diastolic threshold strength and a pulse of 2-ms duration with a pulse generator (BD-02, Fukuda Denshi Co., Tokyo, Japan). An S_1–S_2 interval was applied after 8 beats of drive pacing (S_1) at basic cycle lengths of 600 ms and 400 ms. The S_1–S_2 interval was decreased in 10-ms steps until the effective refractory period of the right ventricle was reached. When polymorphic ventricular tachycardia (VT) or VF lasting >5 s and requiring direct current (DC) shock was not induced with a single premature beat, double or triple extrastimuli ($S_3 \geq 180$ ms and $S_4 \geq 180$ ms) were delivered. Patients with polymorphic VT or VF that did not terminate spontaneously within 5 s and required DC shock for termination were defined having as positive test.

2.5. Follow-up

In general, patient follow-ups occurred at 4- to 5-month intervals and at the time of the event of symptom onset or device discharges at our outpatient clinic. Examinations included an assessment of subjective symptoms, 12-lead ECG, and device interrogation. Follow-ups ranged from 6–194 months (mean, 71.9 ± 89.7 months; median, 67 months).

2.6. Statistical analysis

Continuous clinical and electrophysiological data are shown as mean $\pm$ standard deviation (SD). Intergroup differences in continuous clinical variables were analyzed by Mann–Whitney *U* test, and differences in the presence of ER, symptoms, and family history of sudden cardiac death were analyzed by Fisher's exact probability test. A P value of <0.05 was considered statistically significant. StatView 5.0 software (Statistical Analysis Software [SAS] Institute, Cary, NC, USA) was used for analysis.

3. Results

Of the 69 study patients, 66 were males. The mean age of the 69 patients was 50.2 ± 13.9 years (range, 24 to 76 years). Forty-eight patients showed a spontaneous Brugada type 1 ECG pattern, and 21 showed a drug-induced Brugada type 1 ECG pattern. Clinical, genetic, electrocardiographic, and electrophysiological characteristics of the study group are shown in Table 1. Eleven patients were symptomatic (3 with a history of syncope, 2 with presyncope, and 6 with aborted SCD), and 5 patients had a family history of SCD. An *SCN5A* gene mutation was found in 2 patients (4.5%). The left ventriculogram was normal in all patients, with an ejection fraction of $70.1\% \pm 8.2\%$ (range, 55%–89%). The coronary angiogram was also normal. Programmed ventricular stimulation induced VF/polymorphic VT in 49 patients (89.1%). VF/polymorphic VT was induced by 2 extrastimuli from RVA ($n=15$), RVOT ($n=24$), and both RVA and RVOT ($n=3$); VF/polymorphic VT was induced by 3 extrastimuli from RVA ($n=1$), RVOT ($n=5$), and both RVA and RVOT ($n=1$). An ICD was implanted in 19 individuals (27.5%); 11 symptomatic patients and 8 asymptomatic

Table 1
Baseline clinical, genetic, electrocardiographic, and electrophysiologic data of the present cohort.

Variables	Patients ($n=69$)
Age, years	50.2 ± 13.9 (24–76)
Males	66
Symptomatic	11
Family history of SCD	5
Spontaneous type 1 ECG pattern	48
SCN5A gene mutation	2
ER pattern	7
Late potential	28/61
PR interval in lead II, ms	170.7 ± 22.2
QTc interval, ms	410.5 ± 40.4
QRS duration, ms	105.9 ± 16.11
EPS	55/69
AH, ms	107.2 ± 50.9
HV, ms	49.5 ± 12.4
Inducible VF/PVT at EPS	49/55
ICD implantation	19
Follow-up, months	71.9 ± 89.7 (6–194)
Arrhythmic event during follow-up	2

Data in parenthesis are percents. SCD=sudden cardiac death, BS=Brugada syndrome, EPS=electrophysiologic study, V=ventricular fibrillation, PVT=polymorphic ventricular tachycardia, ICD=implantable cardioverter defibrillator.

patients with inducible VF who elected to receive an ICD implant. An ER pattern was observed in 7 patients (10.1%) with a spontaneous ($n=6$) or drug-induced ($n=1$) Brugada type 1 ECG pattern. No patients associated with ER pattern received Ca^{2+} antagonists or beta blockers. Notched or slurred *J*-point elevation was observed in the inferior ($n=5$, Fig. 1) or both the inferior and lateral leads ($n=2$, Fig. 2). Three of the 7 patients showed day-to-day changes in the amplitude and shape (slurred or notched) of the *J* wave, whereas another 4 patients did not show day-to-day changes in *J* wave morphology. However, none of the 7 patients showed disappearance of the *J* wave in the consecutive ECG recordings. In 6 patients with spontaneous Brugada type 1 ECG patterns, the *J* wave and coved-type ST-segment elevation were present in all ECGs; in 1 patient with drug-induced coved-type ST-segment elevation, the presence of *J* wave and coved-type ST-segment elevation was observed simultaneously only after pilsicainide administration. Late potentials were positive in 3 patients (50.0%) with the ER pattern ($n=6$) and in 25 patients (45.5%) without the ER pattern ($n=55$). The root mean square voltage of the terminal 40 ms in the filtered QRS complex in patients with and without ER was 40.3 ± 6.9 μV and 40.3 ± 10.9 μV, respectively ($P=0.69$), and the duration of the low-amplitude signals <40 μV in the terminal filtered *R* complex with and without ER was 32.0 ± 43.9 ms and 19.0 ± 9.5 ms, respectively ($P=0.80$).

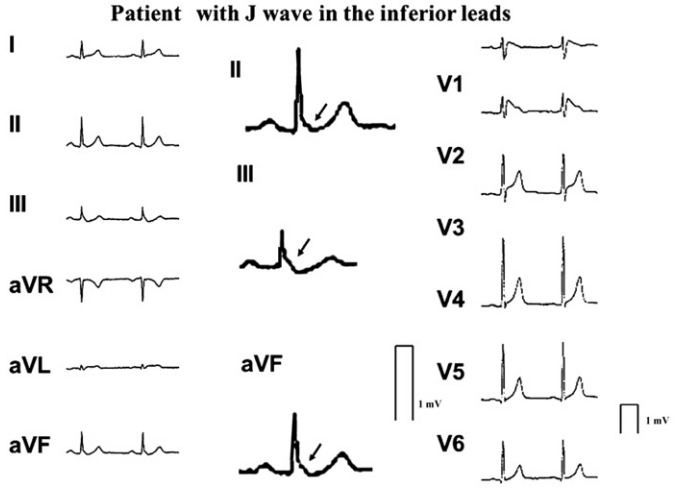

Fig. 1. Notched (or slurred) *J*-point elevation observed in the inferior leads of a patient with a Brugada type 1 ECG pattern.

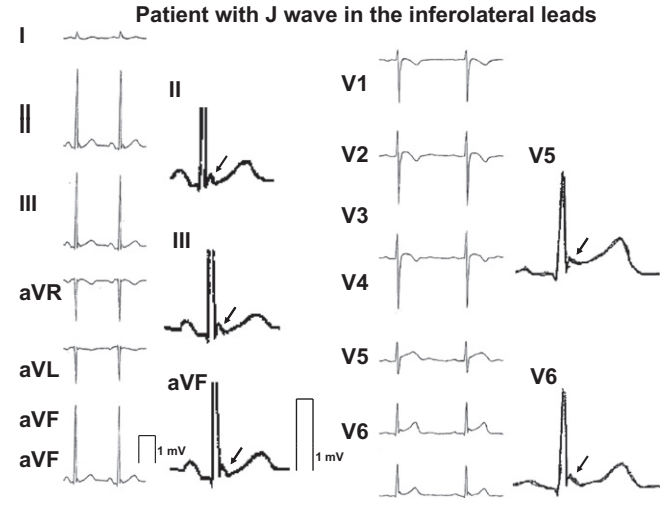

Fig. 2. Notched (or slurred) *J*-point elevation observed in the inferior and lateral leads of a patient with a Brugada type 1 ECG pattern.

Table 2
Baseline clinical, genetic, electrocardiographic, and electrophysiologic data of subjects with and without the ER pattern.

	Patients with ER ($n=7$)	Patients without ER ($n=62$)	*P* value
Age, years	55.6 ± 11.1	49.6 ± 14.1	0.26
Males	7	59	0.83
Symptomatic	1	10	
Family history of SCD	0	5	
Spontaneous type 1 ECG	6	43	0.34
ECG pattern in BS (type 1\2\3)	6/1/0	43/9/10	0.41
Late potential	3/6	25/55	0.97
SCN5A gene mutation	0	2	
PR interval, ms	158.9 ± 17.4	172.0 ± 22.4	0.16
QTc, ms	412.1 ± 26.2	410.3 ± 41.9	0.68
QRS duration, ms	109.7 ± 23.4	105.5 ± 15.3	0.65
EPS	7/7	48/62	0.29
AH, ms	94.7 ± 12.0	109.0 ± 54.1	0.38
HV, ms	45.7 ± 9.1	50.1 ± 12.8	0.44
Inducible VF/PVT at EPS	6/7	43/48	0.89
ICD implantation	4	15	
Follow-up, months	73.6 ± 38.1	67.6 ± 50.8	0.99
Arrhythmic event during follow-up	0	2	

Data in parenthesis are percents. SCD=sudden cardiac death, BS=Brugada syndrome, EPS=electrophysiologic study, V=ventricular fibrillation, PVT=polymorphic ventricular tachycardia, ICD=implantable cardioverter defibrillator.

Clinical, genetic, electrocardiographic, and electrophysiological variables did not differ significantly between patients with and without the ER pattern (Table 2).

3.1. Outcome events

During the mean follow-up period of 71.9 ± 89.7 months, 2 patients with documented VF suffered an arrhythmic event. Neither of these patients had the ER pattern.

4. Discussion

Among our Brugada syndrome patients, the prevalence of the ER pattern was 10.1%, which is high in comparison to the 2%–5% prevalence reported in the general population [1–4]. But similar to the 10%–12% prevalence reported previously in patients with Brugada syndrome [9–11]. Kui et al. reported a higher prevalence of *J* waves (7.26%) in apparently healthy Chinese adults [12]. Uberoi et al. reported that the prevalence of *J* waves in ambulatory clinical population was 2.3%, and *J* waves were more common in individuals of black ethnicity compared to those of Hispanic, white, or other ethnicities [3]. Therefore, it is possible that the prevalence of *J* waves may differ among various ethnicities, although Kui et al. adopted a *J* wave amplitude of >0.05 mV and Uberoi et al. adopted a *J* wave amplitude of >0.1 mV [3]. Thus, the prevalence of *J* waves may be affected by its definition. The clinical implications of Brugada syndrome characterized by ER are controversial. Lantas et al. reported that an ER pattern in inferolateral leads is not an uncommon finding in Brugada syndrome (12%) and found no association between the ER pattern and arrhythmic events during follow-ups in patients with Brugada syndrome (11% with ER vs. 7% without ER, $P=0.223$) [9]. In contrast, Sarkozy et al. reported that patients with Brugada syndrome and an ER pattern in the inferolateral leads were less likely than those without the ER pattern to be asymptomatic at first presentation (13/32 (41%) patients with ER

vs. 156/248 (63%) patients without ER, $P=0.02$) [10]. Kamakura et al. also reported a significantly higher observed frequency of arrhythmic events in Brugada syndrome patients with ER in the inferolateral leads than in those without (7/33 (21%) patients with ER; vs. 17/297 (6%) patients without ER; $P=0.03$) [11].

In the present relatively small single-center study, ER was not associated with adverse outcome events in patients with Brugada syndrome. Antzelevitch et al. hypothesized that an outward shift in the repolarizing current due to a decrease in sodium or calcium channel currents or an increase in I_{to}, IK_{ATP}, IK_{ACh}, or other outward currents can give rise to *J*-wave syndromes, including Brugada syndrome, ER syndrome and hypothermia- and ST-segment elevation myocardial infarction-induced VF [14]. The particular phenotype that manifests depends on which part of the heart is principally affected and which ion channels are involved [14]. However, a recent clinical study reported that patients with idiopathic VF and *J* waves had a high incidence of ventricular late potentials showing circadian variation with night ascendancy, and the authors speculated that *J* waves may be closely associated with depolarization abnormality and autonomic modulation, rather than a repolarization abnormality [15]. Furthermore, Watanabe et al. reported that a reduced heart rate, longer PR and QRS durations, and loss-of-function mutations in SCN5A were found in patients with idiopathic VF and ER; they hypothesized that decreased a sodium current enhances VF susceptibility [16]. In the present study, QRS duration and the prevalence of late potentials did not differ between Brugada syndrome patients with or without ER. Thus, further large-scale clinical and genetic studies are needed to elucidate the pathogenesis of the *J* wave and to assess the prognostic significance of the coexistence of *J* waves in the inferolateral leads of patients with Brugada syndrome.

4.1. Study limitations

The limitations of our study must be taken into account. First, the ECG features of both ER syndrome and Brugada syndrome are dynamic, and therefore the true prevalence of their coexistence is difficult to evaluate. Second, we could not rule out any cause of syncope not related to ventricular tachyarrhythmias. Finally, the overall study group was relatively small, thus the number of arrhythmic events during follow-up may not accurately reflect the prognostic significance of the ER pattern in Brugada syndrome; therefore, a large-scale multicenter prospective study is necessary to evaluate the prognostic significance of *J* waves in the inferolateral leads of patients with Brugada syndrome.

5. Conclusions

This single center study confirmed that the ER pattern in the inferolateral leads is not an uncommon finding in patients with Brugada syndrome. Further, the study showed that the ER pattern is not predictive of adverse outcome events in patients with a spontaneous or drug-induced Brugada type 1 ECG pattern. Future large-scale studies that include high-risk patients are needed to establish the prognostic significance of the ER pattern in Brugada syndrome.

Conflict of interest

The authors have no conflict of interest regarding the study described herein.

References

[1] Shu J, Zhu T, Yang L, et al. ST-segment elevation in the early repolarization syndrome, idiopathic ventricular fibrillation, and the Brugada syndrome: cellular and clinical linkage. J Electrocardiol 2005;38:26–32.
[2] Gussak I, Antzelevitch C. Early repolarization syndrome: clinical characteristics and possible cellular and ionic mechanisms. J Electrocardiol 2000;33:299–309.
[3] Uberoi A, Jain NA, Perez M, et al. Early repolarization in an ambulatory clinical population. Circulation 2011;124:2208–14.
[4] Haïssaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. N Engl J Med 2008;358:2016–23.
[5] Rosso R, Kogan E, Belhassen B, et al. *J*-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. J Am Coll Cardiol 2008;52:1231–8.
[6] Tikkanen JT, Anttonen O, Junttila J, et al. Long-term outcome associated with early repolarization on electrocardiography. N Engl J Med 2010;361:2529–37.
[7] Letsas KP, Efremidis M, Pappas LK, et al. Early repolarization syndrome: is it always benign? Int J Cardiol 2007;114:390–2.
[8] Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation 2005;111:659–70.
[9] Letsas KP, Sacher F, Probst V, et al. Prevalence of early repolarization pattern in inferolateral leads in patients with Brugada syndrome. Heart Rhythm 2008;**5**:1685–9.
[10] Sarkozy A, Chierchia GB, Paparella G, et al. Inferior and lateral electrocardiographic repolarization abnormalities in Brugada syndrome. Circ Arrhythm Electrophysiol 2009;2:154–61.
[11] Kamakura S, Ohe T, Nakazawa K, et al. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V_1–V_3. Circ Arrhythm Electrophysiol 2009;**2**:495–503.
[12] Kui C, Congxin H, Yan-Hong T, et al. Characteristic of the prevalence of *J* wave in apparently healthy Chinese adults. Arch Med Res 2008;39:232–5.
[13] Masaki R, Watanabe I, Nakai T, et al. Role of signal-averaged electrocardiograms for predicting the inducibility of ventricular fibrillation in the syndrome consisting of right ventricular branch block and ST segment elevation in leads V_1–V_3. Jpn Heart J 2002;43:367–78.
[14] Antzelevitch C, Yan GX. J wave syndromes. Heart Rhythm 2010;7:549–58.
[15] Abe A, Ikeda T, Tsukada T, et al. Circadian variation of late potentials in idiopathic ventricular fibrillation associated with *J* waves: insight into alternative pathophysiology and risk stratification. Heart Rhythm 2010;**7**:675–82.
[16] Watanabe H, Nogami A, Ohkubo K, et al. Electrocardiographic characteristics and SCN5A mutations in idiopathic ventricular fibrillation associated with early repolarization. Circ Arrhythm Electrophysiol 2011;4:874–81.